REMARKS

In the Office Action, claims 1-18, 28, 32-36, 38-41, 43-44 and 50-55 are rejected under 35 U.S.C. §103. Claims 14, 28, 32, 33 and 34 are provisionally rejected under 35 U.S.C. §101 for double patenting, and claims 1-18 and 20-28 are provisionally rejected under the judicially created doctrine of non-statutory obviousness-type double patenting. Claim 32 has been amended. Applicants believe that the rejections are improper in view of the amendments and for the reasons set forth below.

Claim 32 has been amended to correct a minor grammatical error. Applicants note for the record that this amendment has been made for clarification purposes only and, thus, are not intended to narrow and/or disclaim any subject matter in view of same.

In the Office Action, claims 1-18, 28, 32-36, 38-41, 43-44 and 50-55 are rejected under 35 U.S.C. § 103 as being unpatentable over *Biochem. J.* (1998) 334, 283-295 to Hennebicq–Reig et al. ("*Hennebicq–Reig*") taken with *J. Nutr.* (1998) 128, 1752-1759 to Bertolo et al. ("*Bertolo*"), U.S. Patent No. 6,468,987 to Demichele et al. ("*Demichele*"), Vet. Record (1987) 121, 557-559 to Pearson et al. ("*Pearson*"), and U.S. Patent No. 6,187,558 to Granados et al. ("*Granados*"). The Patent Office primarily relies on the *Hennebicq-Reig* reference and thus relies on the remaining cited art to remedy the deficiencies of same. Applicants believe that this rejection is improper.

Of the pending claims at issue, claims 1, 8, 14, 20, 24, 28, 32, 35, 40, 50, 51, 52, 53, 54 and 55 are the sole independent claims. Claim 1 relates to a method for treating a disease state characterized by alterations to the mucin levels to a patient. The method includes enterally administering to the patient a nutritional composition which has a protein source including amino acids wherein threonine comprises at least 5.5% by weight of the protein source. Claim 8 relates to a method for maintaining the synthesis of mucins in a patient. The method includes enterally administering to the patient a nutritional composition which has a protein source including amino acids wherein threonine comprises at least 5.5% by weight of the protein source.

Claim 14 recites a method for maintaining a synthesis of mucins in a patient. The method includes enterally administering to the patient a nutritional composition which includes a protein source that contains a therapeutically effective amount of threonine, a carbohydrate

source and a lipid source including a mixture of medium chain triglycerides and long chain triglycerides. Claim 20 recites a method of treating a disease state characterized by alterations to the mucin level in a patient. The method includes enterally administering to the patient a nutritional composition that has a protein source including amino acids wherein threonine comprises at least 7.4% by weight of the protein source. Claim 24 recites a method for maintaining the synthesis of mucins in a patient. The method includes enterally administering to the patient a nutritional composition that has a protein source including amino acids wherein threonine comprises at least 7.4% by weight of the protein source.

Claim 28 recites a method for increasing the synthesis of mucins in a patient. The method includes supplementing a diet of the patient by adding a therapeutically effective amount of threonine to the diet. Claim 32 recites a method for increasing the synthesis of mucins in a patient. The method includes administering to the patient a nutritional composition which has a protein source containing threonine at least 30% of a daily recommended amount of threonine. Claim 35 recites a method of treating intestinal inflammation in a patient. The method includes administering to the patient a therapeutically effective amount of threonine. Claim 40 recites a method for treating intestinal bacterial infection in a patient. The method includes administering a nutritional composition to the patient wherein the nutritional composition contains a therapeutically effective amount of threonine.

Claim 50 recites a method for maintaining the synthesis of mucins in a patient. The method includes enterally administering to the patient a nutritional composition which includes a protein source containing a therapeutically effective amount of threonine. In addition, the nutritional composition includes a carbohydrate source and a lipid source including a mixture of medium chain triglycerides and long chain triglycerides. The protein source provides about 10% to about 20% of the energy of the nutritional composition.

Claim 51-53 recite methods for increasing the synthesis of mucins in a patient. The method of Claim 51 includes supplementing a diet of the patient by adding to the diet a therapeutically effective amount of threonine which is at least 0.2 mM. The method of Claim 52 includes supplementing a diet of the patient by adding to the diet a therapeutically effective amount of threonine which is at least 0.8 mM. The method of Claim 53 includes supplementing

a diet of the patient by adding to the diet a therapeutically effective amount of threonine which ranges from about 0.2 mM to about 0.8 mM.

Claim 54 recites a method of treating intestinal inflammation in a patient. The method includes administering to the patient a therapeutically effective amount of threonine. The threonine is provided as a nutritional supplement which contains threonine in an amount of at least 0.2 mM.

Claim 55 recites a method of treating intestinal bacterial infection in a patient. The method includes administering a nutritional composition to the patient which contains a therapeutically effective amount of threonine. The threonine is provided as a nutritional supplement which contains threonine in an amount of at least 0.2 mM.

As discussed in the previous Response to Office Action filed on October 17, 2003, Applicants have conducted a number of experiments to demonstrate the beneficial effects of the claimed invention. For example, Applicants have demonstrated with both *in vitro* and *in vivo* studies that threonine supplementation can be an effective and efficient nutritional strategy to increase or restore the mucoprotein synthesis rate, and thus to enhance epithelial cell protection. *See*, Specification, Examples 3 and 4, pages 12-13. Further, Applicants have demonstrated that mucus conditions in patients improve after administering the nutritional composition according to an embodiment of the present invention as described in Example 2. In fact, the improved mucus conditions resulted in the remission of diseases such as Crohn's disease in most of the patients who were diagnosed with such disease. *See*, Specification, page 12, lines 5-8.

In contrast, Applicants believe that the cited art, even if combinable, fails to disclose or suggest the claimed invention. The Patent Office relies on *Hennebicq-Reig* as its primary reference as discussed above. More specifically, the Patent Office relies on Table 4 of *Hennebicq–Reig* to support its contention that *Hennebicq–Reig* teaches or suggests that "increasing threonine amount is proportional to enhancing or/and maintaining mucin biosynthesis". Applicants respectfully submit that *Hennebicq–Reig* fails to provide a sufficient basis for such a conclusion.

Contrary to the Patent Office's position, Table 4 of *Hennebicq–Reig* fails to teach or suggest the importance of threonine for mucin synthesis. Table 4 of *Hennebicq–Reig* compares

the amino acid composition of mucins secreted by genetically altered control cells and genetically altered cells that have been treated with the O-glycosylation inhibitor. The Patent Office reasons that, because *Hennebicq–Reig* discloses a threonine level in each of these mucins to be the highest among the other amino acids, *Hennebicq–Reig* allegedly teaches or suggests increasing and/or maintaining mucin biosynthesis by increasing the amount of threonine. In its discussion of the results of Table 4, *Hennebicq–Reig* merely states that "[t]he chemical composition of the mucin fraction is given in comparison with the control HT-29 MTX mucin fraction (Table 4). Only slight changes in amino acid composition were found in mucins of treated cells." *See Hennebicq–Reig,* page 287, second column). As disclosed in Table 4, this reference merely shows that threonine is a significant component of mucin. Clearly, this does not suggest that increasing threonine levels would result in a proportional increase in mucin biosynthesis as suggested by the Patent Office. Indeed, other factors such as the bioavailability of that component as well as other constituent components may play an important role.

Moreover, the cells in *Hennebicq–Reig* were not exposed to differing concentrations of threonine to determine if such a relationship exists. Indeed, the primary focus of *Hennebicq–Reig* relates to the effects of an inhibitor of O-glycosylation (a benzyl-N-acetyl-α-D-galactosaminide) on the structure of oligosaccharide chains attached to the threonine and serine residues of mucin secreted by malignant epithelial cells exposed to the anti-cancer drug, methotrexate (designated by HT-29 MTX). As disclosed by *Hennebicq–Reig,* these cells have altered expression of mucin genes which leads to an abnormal profile of mucin production along with other changes in the biochemical characteristics of mucins. *See Hennebicq–Reig* page 283, column 2, paragraph 2. Although the inhibition of O-glycosylation by the galactosaminide occurs on threonine residues, *Hennebicq–Reig* fails to disclose a relationship between threonine availability and mucin synthesis. Therefore, *Hennebicq–Reig* provides no motivation to determine whether increasing threonine levels would result in a proportional increase in mucin biosynthesis. In contrast, Applicant has demonstrated that increasing the bioavailability of threonine in the culture medium can significantly increase mucoprotein synthesis in vitro as previously discussed. See, specification, Example 3. Thus, the *Hennebicq-Rei*g reference, on its own, is clearly deficient with respect to the claimed invention.

Further, Applicants believe that the Patent Office cannot rely on the remaining cited art, separately or in any hypothetical combination, to remedy the deficiencies of the primary reference as discussed above. For example, *Bertolo* is deficient with respect to maintaining or increasing the synthesis of mucins in a patient by enterally administering to the patient a nutritional composition which has a protein source including amino acids wherein threonine includes at least 5.5% by weight of the protein source as required by the claimed invention.

Bertolo relates to threonine requirements of a very specialized group of neonatal piglets undergoing total parenteral nutrition (TPN). *See Bertolo,* page 1752, column 2. Specifically, *Bertolo* attempts to determine optimal threonine levels required under such circumstances. *Bertolo* provides that threonine requirements are reduced when mucin production is reduced as a result of goblet cell atrophy during TPN feeding of neonatal piglets. Yet, this teaching fails to suggest that the mucin level can be maintained or increased by supplementation of a threonine source as claimed. Indeed, *Bertolo* proceeds to disclose other factors related to a decrease in a threonine requirement in neonatal piglets on TPN such as "[h]ormonal modulation of nutrient metabolism". See *Bertolo* page 1758, column 1, paragraph 3. Moreover, the alleged relationship between mucin production and threonine requirement disclosed in *Bertolo* is in the context of administering nutrition into the circulation unlike the claimed invention which relates to enterally administering a nutritional composition, such as into the gastrointestinal tract. Clearly, an enteral formulation for treating problems of reduced mucin synthesis as required by the claimed invention is distinguishable from the requirements of neonatal piglets undergoing parenteral nutrition.

The Patent Office also relies on *Bertolo* to support its conclusion that a nutritional composition having a protein source which includes a hydrolyzed sweet whey protein would have been obvious as required by claims 3, 9-10 and 16-17 of the claimed invention. The Patent Office refers to *Bertolo*'s reference to the constituents of the TPN administered to the neonatal piglets which includes amino acids, glucose, and lipids. See *Bertolo,* page 1753, column 1, paragraph 4. Clearly this is improper, and as such, *Bertolo* fails to disclose or suggest enterally administering a nutritional composition let alone a nutritional composition that includes a protein source which includes a sweet whey protein as further required by the claimed invention.

The Patent Office further relies on *Bertolo* to support its conclusion that it would have been obvious to increase the synthesis of mucins in a patient by administering to the patient a nutritional composition which has a protein source containing threonine at least 30% of a daily recommended amount of threonine as required by claims 32-34 of the claimed invention. According to *Bertolo*, it was hypothesized that the mean threonine requirement of orally fed neonatal piglets was 0.58 g/kg·d (page 1756). On the basis of this, the threonine requirement of parenterally fed neonatal piglets was predicted to be 0.4-0.5 g/ kg·d (page 1757, column 1). However, *Bertolo* actually determined the threonine requirement of parenterally fed neonatal piglets to be 0.19 g/ kg·d (see column 2, paragraph 1 on page 1757-- "the predicted threonine requirement for TPN-fed piglets of 0.4-0.5 g/(kg·d) was more than twice the mean requirement of 0.19 g (kg·d) determined in this study"). To compare the experimentally determined mean threonine requirement for orally fed piglets with the predicted mean threonine requirement for parenterally fed piglets (which, in any event, turned out to be wrong) to arrive at a daily recommended amount of threonine to be 110% is improper since both amounts would be a daily requirement for different methods of feeding. Therefore, clearly *Bertolo* is deficient with respect to a method for increasing the synthesis of mucins in a patient which includes administering to the patient a nutritional composition which has a protein source containing threonine at least 30% of a daily recommended amount of threonine as required by the claimed invention.

Bertolo also is deficient with respect to an amount of threonine of at least 0.2 mM as further defined by the claimed invention. The threonine content of 1732 μmol/1 for enteral feeding as disclosed in *Bertolo* is a plasma concentration; whereas, the amount of threonine recited in Claims 51-55 of at least 0.2 mM is the concentration of threonine in the composition. Indeed, Applicants have demonstrated in Example 3 a significant increase in the fractional synthesis rate of microproteins when a diet is supplemented with at least 0.2 mM threonine as previously discussed. Therefore, Applicants respectfully submit that *Bertolo*, even in combined with *Hennebicq–Reig*, is distinguishable from the claimed invention.

Demichele is similarly deficient with respect to the claimed invention. For example, nowhere does this reference disclose or suggest that a therapeutically effective amount of threonine can be administered to the patient in order to treat disease in the patient that can alter mucin levels as required by the claimed invention. The primary focus of *Demichele* relates to

the use of a composition that includes indigestible carbohydrates and poly-unsaturated fatty acids in the treatment of ulcerative colitis. This reference suggests that these two components can act together to promote the incorporation of small n–3 fatty acids into colonocytes at the expense of n–6 fatty acids thereby increasing the rate of the incorporation of the n–3 series into the colonic mucosal phospholipids, thus modulating the rate of local eicosanoid generation by the gastrointestinal mucosa. Threonine, however, is not involved in the process disclosed in *Demichele* that relates to the modulation of local eicosanoid generation by the cells of the gastrointestinal mucosa. Therefore, while local eicosanoid generation by the gastrointestinal mucosa may be modulated by diet, thereby reducing inflammation as *Demichele* purportedly suggests, this modulation is a completely different mechanism of operation from the synthesis of mucins (e.g., the main component of the substance which protects the gastrointestinal mucosa) promoted by the administration of a therapeutically effective amount of threonine. Therefore, *Demichele* fails to recognize the importance of administering a therapeutically effective amount of threonine to a patient to treat disease in the patient in contrast to the claimed invention.

The Patent Office also relies on *Demichele* in an attempt to cure the deficiency of the other references with respect to a protein source which includes whey protein. However, *Demichele* fails to disclose or suggest a protein source including amino acids wherein threonine comprises at least 5.5% by weight of the protein source as suggested by the Patent Office. The Patent Office relies on the disclosure in *Demichele* of a 75% whey protein concentrate and the disclosure in the specification of the Applicants of a threonine content of 7.4% by weight of amino acids in sweet whey protein to determine the amount of threonine disclosed in *Demichele*. As pointed out in Applicants' Response to the previous Office Action, however, the Patent Office's calculation contradicts what *Demichele* discloses. For example, Table 12 shows that the threonine content of the product taught in *Demichele* is 4.34% of the amino acids. Clearly, this is below the amount of threonine as required by the claimed invention and as such, effectively teaches away from same.

Moreover, even if a calculation can be performed to determine the amount of threonine in the composition disclosed in *Demichele*, the Patent Office's calculation is inaccurate. Contrary to what is suggested by the Patent Office, the protein source in the composition disclosed by *Demichele* does not contain 75% whey protein. Instead, *Demichele* discloses adding to the

composition "the 75% whey protein concentrate". *See Demichele*, column 17, lines 54-55. It is known in the art that whey protein concentrates are not 100% protein and can range in concentration from 50 to 90% whey protein. Therefore, whey protein does not constitute 75% of the product in *Demichele*. Rather, the protein source in *Demichele* includes a whey protein concentrate containing 75% protein. In fact, according to Table 14, the 75% whey protein concentrate only constitutes 6% of the protein source of the *Demichele* composition which also includes sodium caseinate – 1427.04 kgs., partially hydrolyzed caseinate – 1427.04 kgs., and soy polysaccharide – 85.28 kgs.. See *Demichele*, column 17, lines 45-59. Therefore, even if a calculation can be performed as the Patent Office suggests, the 75% whey protein concentrate of *Demichele* would only include about 0.3% threonine (6% x 75% x 7.4%). Regardless, the percentage of threonine in the protein source disclosed in *Demichele* is much less than the 5.5% by weight of the protein source as required by the present invention as discussed above. Indeed, Applicants have demonstrated in Example 1 increased mucin levels in rats fed a sweet whey diet containing threonine which is at least 5.5% by weight of the protein. Therefore, Applicants respectfully submit that *Demichele*, at a minimum, is distinguishable from a protein source including amino acids wherein threonine includes at least 5.5% by weight of the protein source as required by Claims 1, 3-4, 15-17, 35-36, 38-41 and 43-44. Based on at least these reasons, Applicants believe that *Demichele* is distinguishable from the claimed invention, even if combinable with the remaining reference in any hypothetical combination.

Granados cannot be relied on solely to remedy the deficiencies of the other cited art. For example, *Granados* fails to teach or suggest a method of treating intestinal bacterial infection in a patient by administering a nutritional composition to the patient wherein the nutritional composition contains a therapeutically effective amount of threonine. As previously noted, *Granados* is related to insect mucins. Although, the first two paragraphs of *Granados* cited by the Patent Office discuss the role played by mucus in vertebrates, the following paragraph in *Granados* states "[s]tudies on invertebrate mucins are very limited by comparison with vertebrate mucins". The fourth paragraph in *Granados* further provides that "part of the reason for this may be that insects do not possess a mucus layer lining the digestive tract and/or other epithelial cells as do vertebrates". Applicants respectfully submit that such statements would constitute a teaching away from the claimed invention, and that one skilled in the art would not

be motivated to combine and/or alter the other cited art in view of *Granados*. Furthermore, novel insect mucin disclosed in *Granados* may be rich in threonine, but it also contains similar amounts of proline and alanine which are not significant substituents in human mucus. *See Granados*, column 4, lines 42-45. Therefore, *Granados* fails to teach or suggest a method of treating intestinal bacterial infection in a patient by administering a nutritional composition to the patient wherein the nutritional composition contains a therapeutically effective amount of threonine as required by claims 40-44 of the claimed invention even if combinable with the other cited art.

With respect to *Pearson*, the Patent Office purportedly asserts that a disease state characterized by alterations to the mucin levels would have been obvious. To make this assertion, the Patent Office improperly equates alterations to the mucin levels with damage to the mucosal layer by an ulceration. *Pearson*, however, merely suggests that alteration in mucin depth and focal mucin depletion may lead to mucosal damage, a disease state. *See Pearson* page 559, column 2, paragraph 2. As Applicants have already acknowledged in the Specification, page 2, lines 3-8, ulcerative colitis is known to be associated with alterations in mucin synthesis. Therefore, the teaching in *Pearson* provides little, if any additional, understanding to what is known in the art. More importantly, *Pearson* fails to teach or suggest a method of treating a disease state characterized by alterations to the mucin levels in a patient by enterally administering to the patient a nutritional composition which has a protein source including amino acids wherein threonine comprises at least 5.5% by weight of the protein source and, thus, is distinguishable from the claimed invention even if combinable with the other references.

As previously discussed, the references cited by the Patent Office each fail to motivate one skilled in the art to combine and/or modify the teachings of the references to reconstruct the claimed invention. Instead, the Patent Office has relied on hindsight knowledge of the claimed invention, thus using the claimed invention as a template for the reconstruction of its elements. Indeed, the Patent Office attempts to combine and/or modify up to five references from different backgrounds to piece together the claimed invention. For example, *Hennebicq-Reig* which relates to an in vitro investigation into the structure of mucins secreted by malignant epithelial cells which have been treated with the anticancer drug methotrexate, is purportedly combined with *Bertolo* which relates to how to calculate the amount of threonine required by neonatal

piglets receiving total parenteral nutrition as opposed to normal enteral nutrition. The Patent Office bases the combination of *Bertolo* with *Hennebicq-Reig* on their alleged common teaching that threonine plays an essential role in maintaining mucin protein synthesis. As discussed above, *Hennebicq-Reig* fails to suggest the importance of threonine for mucin synthesis. Indeed, the technical aspects as disclosed in the *Hennebicq-Reig* and *Bertolo* references are very different and, thus, would not lead one skilled in the art to combine, let alone modify same, based on these differences.

The Patent Office further combines other unrelated references to cure the deficiencies of the combination of *Bertolo* with *Hennebicq-Reig*. Elements from *Demichele* which relate to nutritional products for treating ulcerative colitis, elements from *Granados* which relate to insect mucins and elements from *Pearson* which relate to mucosal changes associated with ulceration in calves are used to reconstruct the claimed invention. Even if combinable, the purported teachings provide an insufficient basis to remedy the deficiencies of *Bertolo* and/or *Hennebicq-Reig* as discussed above. Therefore, Applicants do not believe that one skilled in the art would be inclined to modify the cited art to reconstruct the claimed invention.

Based on at least these noted reasons, Applicants believe that the cited art fails to disclose or suggest at least a number of features of the claim invention. Therefore, Applicants respectfully submit that the cited art, even if combinable, fails to render obvious the claimed invention.

Accordingly, Applicants respectfully request that the obvious rejection be withdrawn.

Claims 14, 28, 32, 33 and 34 are provisionally rejected under 35 U.S.C. §101 for double patenting in view of pending U.S. Application No. 10/182,854. At this time, the rejection is provisional. Upon the issuance of a patent for the present application or U.S. Application No. 10/182,854, Applicants intend to amend and/or cancel any claims deemed conflicting pursuant to 35 U.S.C. §101 if required at such time. Therefore, Applicants believe they have been responsive to this double patenting rejection.

Claims 1-18 and 20-28 are provisionally rejected under the judicially created doctrine of non-statutory obviousness-type double patenting in view of pending U.S. Application No. 10/182,854. At this time, the rejection is provisional. Upon the issuance of a patent for the present application or U.S. Application No. 10/182,854, Applicants intend to file a terminal

disclaimer in compliance with 37 C.F.R. 3.73(b). Therefore, Applicants believe they have been responsive to this double patenting rejection if required at such time.

For the foregoing reasons, Applicants respectfully submit that the application is in condition for allowance and earnestly solicit reconsideration the same.

Respectfully submitted,

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